

## Letter to the Editor

### Response to Dr C. Daniel Mullins' letter [re: *Osteoarthritis and Cartilage*, 2002; 10:518–27]

We are pleased that Dr Mullins found our study worthy of applause, and one that fills a gap in available information regarding therapeutic approaches to the management of patients with knee OA. Indeed, the study was designed and executed as rigorously as possible, and represents, in our opinion, not only valuable scientific information for the management of patients with knee OA, but also a useful teaching example of good methodology for the design and analysis of pragmatic, health outcomes, and cost-effectiveness trials.

We also thank Dr Mullins for raising a number of questions and providing us the opportunity to respond.

#### Non-inclusion of COX-2 specific inhibitors

At the time of study initiation (1997), the new generation of COX-2 specific inhibitors were not yet licensed for use in North America. The ACR Guidelines which defined the treatment paradigm for the appropriate care (AC) arm of the study were those published in 1995<sup>1</sup>.

We are happy to address the conjectural question raised by Dr Mullins, regarding how the results of the study might have changed if the currently available COX-2 specific NSAIDs had been available at that time.

With respect to clinical effectiveness, we believe the incremental improvement we observed for the appropriate care+hyaluron G-F 20 (AC+H) arm might be expected to persist had COX-2 specific agents been available during our study. This speculation is based on the fact that COX-2 specific agents have not demonstrated improvement in pain relief compared to generic NSAIDs<sup>2</sup>.

With respect to safety, it is possible that the statistically significant and clinically important decrease in treatment-related GI adverse events reported for the AC+H arm in our trial might not have been observed had COX-2 specific inhibitors been available during the study. However, because these two NSAID classes differ with respect to the number and type of associated adverse events and the debate continues regarding their overall safety profile and drug interactions<sup>2,3</sup>, it is difficult, on balance, to predict how the availability of these agents might have changed the systemic safety outcomes of our study.

With respect to costs, we would expect that the mean annual cost per patient would have increased more in the AC arm than the AC+H arm. This conjecture is based on the greater NSAID usage in the AC arm ( $p=0.0062$ ) of our

study and the higher acquisition costs of COX-2 specific agents.

In summary, we speculate that the cost-effectiveness and cost-utility of adding hyaluron G-F 20 to the treatment paradigm would have at least remained comparable, and might even have improved, had COX-2 specific agents been available during our study.

#### Cost differences in cost categories

Dr Mullins is puzzled by the directions of the cost differences in a number of cost categories. To this we have two comments. First, the study was designed to measure overall costs and compute overall cost-effectiveness and cost-utility results. It was not designed or powered to investigate cost differences at the level of cost categories. To do so is akin to performing post hoc sub-group analyses and has the same methodological weaknesses. That is, the comparisons should be adjusted for multiple testing, and any statistically significant results are, at best, hypothesis generating.

Nevertheless, and second, we provide here some comments and elaborations on these cost differences. Dr Mullins noted that the group treated with hyaluron G-F 20 (AC+H) had lower costs of medications for knee OA (e.g., NSAIDs). This difference was substantial (46% lower) and was presumably due to the beneficial effect of the hyaluron G-F 20 treatment. In contrast, as Dr Mullins noted, the group treated with hyaluron G-F 20 had higher costs of treating adverse events due to OA treatment. This difference, however, was slight (8% higher) and given the very large standard deviations would not come close to approaching statistical significance. Moreover, the details of this cost category show it to be composed of a wide variety of medications (23 different kinds of medications as coded by anatomic therapeutic classification (major code) and by drug indication (minor code) using the 1999 Compendium of Pharmaceuticals and Specialties (CPS; Canadian Pharmaceutical Association) and, the number of actual medications (i.e., drug treatments) for the AC+H group was 81 while that for the AC group was 86. Thus, we conclude that the minor difference in this cost category was due to chance, and is not a meaningful difference that deserves an interpretation.

Dr Mullins notes that hospitalization costs were higher in the treatment group. As we explained in the article this came about because of our broad inclusion criteria for relevant hospitalization costs. We included the costs of all hospitalizations attributed to OA (in any joint). In the base

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case analysis there were a total of five patients requiring hospitalization attributable to OA in the AC+H group and three patients in the AC group. The five patients in the AC+H group had: total knee replacement in the study knee, total knee replacement in the other knee, total hip replacement, triple ankle fusion, and tibia osteotomy. The three patients in the AC group had: total knee replacement in study knee, total knee replacement in other knee, and bunionectomy. Interestingly, there were two additional hospitalizations in the AC group (both representing total knee replacements in the study knee) that were not counted in the base case analysis because they occurred after the two patients in question had violated protocol.

Finally, Dr Mullins notes that costs for essentially every category of indirect costs (i.e., time lost from work and transportation costs) were higher in the AC+H group. As we explained in the article this was due to the visits needed for the hylan G-F 20 injections.

### Local AEs to hylan G-F 20

Dr Mullins raises safety concerns regarding local reactions after the administration of hylan G-F 20. We would point out that acute inflammatory reactions can occur with all intra-articular treatments including hyaluronan<sup>4</sup> and corticosteroids<sup>5</sup>. Reports as to the prevalence of such reactions vary widely<sup>6</sup>.

Dr Mullins cites a recent publication, which purports to show that the rate of local reactions after hylan G-F 20 injection increases from 2 to 21% when comparing first and second courses of treatment. This publication compares a cohort of patients who received their first course of hylan G-F 20 as part of a clinical trial, to an unrelated retrospective cohort who received their second course during routine medical practice. Though we will not address the methodology used in this citation, we can comment on the prevalence of adverse reactions during repeat courses of hylan G-F 20 treatment in our trial. Repeat treatment was permitted by our study protocol because of its pragmatic design, and was administered to 48 patients. These recently presented data<sup>7</sup> found that the prevalence of local reactions attributed to hylan G-F 20 by the investigators to be 1.7% during first courses and 2.9% during second courses. There was no statistically significant difference in the percentage of patients reporting local adverse reactions between the first course subgroup and the first course of treatment in the second course subgroup. Similarly, there was no statistically significant difference between the first course of treatment and second course of treatment in the second course subgroup.

In summary, we believe that our study provides data that demonstrate the favorable risk-benefit relationship for intra-articular injections of hylan G-F 20 compared to other treatments for OA, during both first and second courses of treatment. Though local reactions can and do occur, we believe the safety of hylan G-F 20 compares favorably to other available treatments for knee OA.

### Costs associated with the management of adverse reactions

Dr Mullins indicates that "It is not clear if Torrance and colleagues have considered the potentially significant medical costs associated with the management of these adverse reactions in clinical practice and/or hospital set-

tings as well as the indirect costs of these adverse reactions as part of the projected cost of hylan G-F 20 therapy". The answer is yes indeed, that is exactly what we considered. We apologize if the manuscript was not clear on that point. Patients were instructed to report *all* health care resource utilization and *all* time lost and expenses regardless of the health reason. Those attributable to OA, to the treatment of OA, or to the side effects or adverse events of the treatment of OA were included in the analysis.

We thank Dr Mullins for his interest in our work, and for the opportunity to respond to his questions. We believe our study definitively supports the 2000 revision of the ACR guidelines<sup>8</sup>, which include intra-articular therapy with hylan G-F 20 as part of the treatment paradigm for patients with knee OA.

### References

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